Long-term results of cyanoacrylate closure for the treatment of incompetent saphenous veins: A German multi-center experience

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Objective: Endovenous techniques have proven to be effective for treatment of incompetent truncal veins (GSV/SSV). The non-tumescent, non-thermal and non-sclerosant VenaSeal™ closure technique has become an established treatment modality, but reports focusing on long-term follow-up are rare.

Methods: A multicenter review of four German outpatient surgery centers, using Cyanoacrylate Closure (CAC, VenaSeal™) for the treatment of incompetent saphenous veins over a period of eight years, was launched.

Results: A total of 2982 patients with a total of 5333 incompetent truncal veins (GVS/SSV) were enrolled. Follow-up ranged from 10 days up to 98 months with a target vein closure rate of maximum 96 %. Accidental glue extension in limited amounts was observed in 0,17% of the limbs. One venous thrombosis (0,01%) occurred due to deep vein valve damage by SELDINGER guide wire. The maximum diameter of glued veins attained 19 mm. There was no need for adjunctive procedures. Miniphlebectomies were carried out in fewer numbers according to center-specific standards. If sclerotherapy was scheduled it was carried out in the first three months post intervention. Compression was not standardized in the after treatment, if necessary, then 7 to 10 days. As a typical side effect, circumscript inflammatory reddening of the skin in areas surrounding the saphenous bed in distal parts of the thigh was observed in 9,3% of patients. This occurred predominantly within the first 14 days after treatment in subdermal truncal veins and responded easily to local anti-inflammatory measures.

Conclusion: Treatment with CAC was effective in achieving complete target vein closure of the GSV and SSV at long-term follow-up. CAC resulted in low postoperative discomfort, early rehabilitation and recovery even in patients who after a few days returned to work or were otherwise burdened by prolonged orthostatic charge.

Key Words: *Cyanoacrylate closure; Saphenous vein incompetence; Long-term outcomes; Multicenter review; Cyanoacrylate long-term follow-up*

INTRODUCTION

Chronic venous incompetence in the adult population shows an incidence of varicose veins in the range of 20% to 60% [1-5]. While conventional surgery has been unquestioned as routine approach to varicose veins throughout the past century, more recently endovascular techniques have proven both safety and efficacy for treatment of incompetent truncal veins (GSV/SSV) in an outpatient setting [6-13]. Tumescence anaesthesia is required using ELVES or RFA by the risk of thermal damage to surrounding tissues like concomitant nerves, lymphatic vessels or overlaying skin. Moreover DVT is observed upon a laser ablation in 0.5% to 7%. On this basis, the CAC technique was developed as a non-thermal and non-tumescent alternative. Cyanoacrylate closure (CAC, VenaSeal™) enables to further reduce postprocedural discomfort in addition to earlier recovery even in patients who are unwilling or unable to undergo tumescent or general anaesthesia and/or mandatory postoperative compression therapy [14-19]. Recent reviews showed target vein closure rates at 12 months ranging from 87% to 97% [20,21]. The aim of this multicenter review was to evaluate whether CAC can deliver long-term effectiveness and safety.

The basis of our review was an eight-year surveillance of patients with Great Saphenous Vein (GSV) and Small Saphenous Vein (SSV) incompetence or a combination of these [22-25]. Furthermore, we wanted to focus the discussion on missing long-term results and controversial technical issues.

CASE STUDY

This review was conducted in four centers as a review in the effectiveness and safety of VenaSeal™ for GSV and SSV incompetence. The baseline examination included a physical examination and duplex ultrasound examination of both legs. Enrolled patients showed symptomatic moderate to severe GSV and SSV incompetence classified by CEAP criteria (Clinical, Etiology, Anatomy, and Pathophysiology classification). Postprocedural complications were defined as occurring within 30 days. Major complications included venous thrombosis, nerve damage and Post Ablation Glue Extension (PAGE). A failure of treatment was defined as a recanalization of more than 5 cm beginning in the saphenofemoral/saphenopopliteal junction. After the procedure, patients visited the center usually on day 10 and at months 3, 12, 36 and 60. Long-term experience exceeded 60 months in center two (79 months) and in center four (98 months) as shown in Table 1.

TABLE 1

Overview of: Baseline data, follow-up and complications stratified by center

Center / Period of interventions		Total 8/2012-10/2020	1 6/2013-10/2020	2 11/2013-10/2020	3 10/2016-10/2020	4 8/2012-10/2020
Total no. of patients		2982	161	832	523	1466
Total no. of treated veins(gsv/ssv)		5333	217	1465	805	2846
Age, years		55,3 (16-95)	56,1(27-85)	54,3(16-95)	55,3 (16-92)	55,5 (17-94)
Clinical class (CEAP)	C2, C2s	51,80%	87	501	234	%
	C3	34,20%	42	289	212	%
	C4a	9,40%	24	73	52	%
	C4b	2,80%	7	24	14	%
	C5	1,80%	1	16	11 (incl. 4×C6)	16

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Technical success rate	After 10 days	5265/5333=98,7%	217/217=100%	1465/1465=100%	805/805=100%	2778/2846=97,61%
	After 3 months	4493/4579=98.1%	114/115=99,1%	1405/1405=100%	798/799=99,9%	2176/2260=96,28%
	After 12 months	3740/3876=96,5%	72/76=94,7%	1371/1382=99,2%	533/542=98,3%	1764/1876=94,03%
	After 36 months	1221/1254=97,4%	26/30=86,7%	201/206=97,6%	127/132=96,2%	867/886=97,9%
	After 60 months	1484/1584=95,9%	13/18=72,2%	114/118=96,6%	%	1357/1412=96,1%
	Longest period	98 months 596/620=96,1%	77 months	79 months 69/72=95,8%	48 months 42/45=93,3%	98 months 596/620=96,1%
Inflammation/reddening in the first 14 days post treatment		497/5333=9,3%	36/217=15,9%	160/1465=10,9%	89/805=11,1%	212/2846=7,5%
Nerve damage		0	0	0	0	0
DVT post treatment (30 days)		1/5333=0,01%	0	1/1465=0,06%	0	0
PAGE(=Post Ablation Glue Extension)		9/5333=0,17%	4/217=1,8%	2/1465=0,13%	3/805=0,37%	0

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Treatment modalities

Patients were treated in the supine position (GSV) or in the Stomach Position (SSV). The standard operation procedure occurred with an assessment of the target saphenous veins (GSV/SSV) by ultrasound. The incompetent SV was punctured under ultrasound guidance and a 0,035" 180 cm J-wire was advanced in the lumen of the vein and positioned in front of the junction to deep vein confirmed by ultrasound. The catheter tip was positioned 2-5 cm caudal the junction according to the Instructions For Use (IFU). The vein was closed completely by pressure with the transducer in cross-sectional view 2 cm below the junction. As the glue spreads for some distance upon release, the vein and insufficient cross veins were closed to this point. More experienced therapists shortened this to 1 cm distance to the junction and thus achieve a smooth finish at the junction. The position of the white delivery catheter tip was verified by ultrasound imaging. Sonographic visibility of the delivery catheter is eased by incorporated echogenic markings (Figures 1-3).

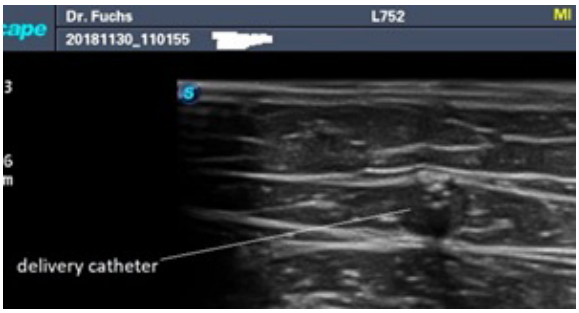

Figure 1) *Sonographic visibility of the delivery catheter is eased by incorporated echogenic markings.*

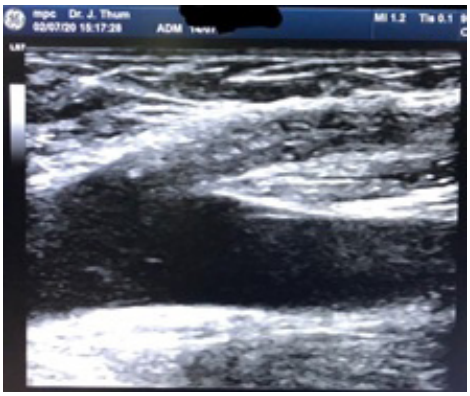

Figure 2) *Therapists shortened this to 1 cm distance to the junction.*

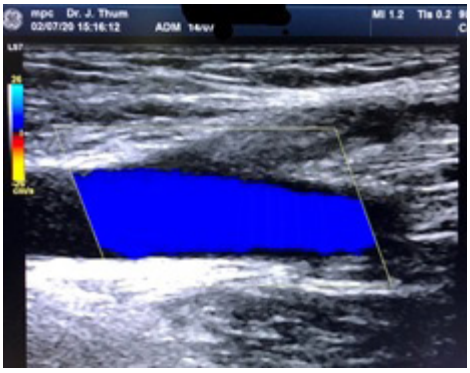

Figure 3) *Smooth finish at the junction.*

While applying pressure with the transducer in front of the catheter tip near the junction the cyanoacrylate adhesive (0.1 ml aliquots) was delivered twice, 10 mm apart, followed by hand compression at the treated segment for three minutes. After verification of reflux-free closure of the vein and insufficient cross veins, subsequent 0.1 ml aliquots of cyanoacrylate were delivered at 30 mm intervals along the target treatment area, and compression with the ultrasound probe and free hand was held for 30 seconds at each treated segment. Additional aliquots of glue were administered if required. Similarly, injections could be given during treatment at the site of tributaries or focal dilatation. When the white delivery catheter is visible, a final injection is administered and the catheter removed. Anatomic success was defined as occlusion of the treated GSV/SSV segment, objectified by duplex ultrasound. The patency of the deep venous system was verified and documented. Adjunctive procedures like concomitant miniphlebectomies were performed in fewer numbers following center-specific standards. If sclerotherapy was scheduled, it was carried out in the first three months post procedure. Compression was not standardized in the aftertreatment. If necessary, then 7 to 10 days. According to the retrospective nature of data collected, there was no comparative statistical-work-up.

RESULTS

Between August 2012 and October 2020 there were 2982 patients with 5333 incompetent truncal veins (GSV/SSV) treated. Baseline characteristics are shown in Table 1. Enrolled patients were 16 to 95-years of age. The majority of them (86,0%) were assigned to class C2 or C3. Forty-four patients (1,8%) had a healed ulcer. A total of 1584 patients consented and completed a 60-month follow-up visit. Clinical success was 95,9% after 60 months. The diameter of treated truncal veins was a maximum 19 mm. One extraordinary case was a venous aneurysm placed in the saphenofemoral conjunction, diameter 23 mm (Figure 4).

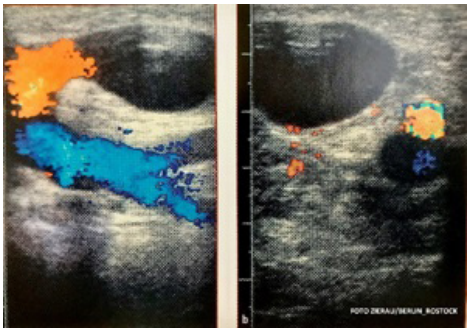

Figure 4) *Venous aneurysm placed in the saphenofemoral conjunction, diameter 23 mm.*

As a typical side effect, a circumscribed inflammatory reddening of the skin in an area surrounding the saphenous bed in distal parts of the thigh was observed in 93% of patients, mainly within the first 14 days after treatment (Figure 5).

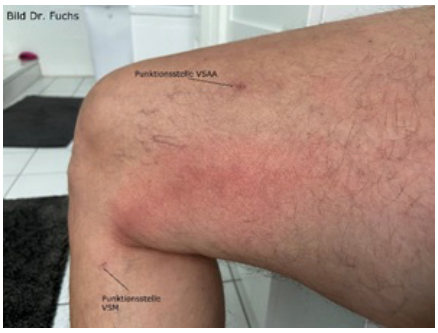

Figure 5) *Reddening of the skin in an area surrounding the saphenous bed in distal parts of the thigh.*

Overall, the complication rate was without procedure-related serious adverse events. No nerve damage was seen in 5333 procedures. An allergic reaction was experienced in one patient with exanthema. The patient had complete recovery after six days of steroids.

Accidental glue extension in limited amounts was observed in 0,17% of the limbs. One deep venous thrombosis occurred (0,01%) due to deep vein valve damage by SELDINGER guide wire. If sclerotherapy was scheduled, it was carried out in the first three months post intervention. Compression was not standardized in the after treatment. No signs of pulmonary embolism were seen. Postoperative use of analgetics and unfitness for work were minimal, even in professionals exposed to orthostatic stowage.

DISCUSSION

The treatment of incompetent truncal veins has undergone a shift towards endovenous procedures during the last decades. In recent years, thermal endovascular techniques were challenged by reports indicating an even lower procedural risk associated with non-thermal chemoablation of truncal veins. Unless extended follow-up data from the VeClose controlled randomized study have been published recently demonstrating noninferiority of CAC compared with RFA, there is persisting uncertainty concerning long-term efficacy and side-effects of the procedure. In our clinical practice, application of cyanoacrylate glue resulted in favourable results in GSV, SSV and accessory saphenous veins comparable to laser or radiofrequency ablation even after five years of follow-up. By use of the CAC, we appreciated dispensing general anaesthesia and reducing or even eliminating compression therapy in the aftertreatment. In multimorbid patients, there was additional profit arising from chemoablation since anticoagulant medication was continued while tumescent or general anaesthesia could be spared. There were no limitations with regard to dosage or number of veins being treated simultaneously. Moreover, we feel that the adhesive is the most reliable and robust technique to withstand early orthostatic charge during the early postoperative period which may cause discomfort and prolong unfitness for work.

Along with alarming case reports and apprehensive data from animal experiments, concern was raised regarding allergic, inflammatory or septic reactions to cyanoacrylates in different use [26-31].

There are variations on the compound n-butyl-cyanoacrylate for medical applications. Three compounds are currently available: 2-Octyl-Cyanoacrylate, marketed as Dermabond® or SurgiSeal®, n-Butyl-2-Cyanoacrylate as Histoacryl®, or Ethyl-2-Cyanoacrylate available as Epiglu®. Allergic contact dermatitis to 2-Octyl-Cyanoacrylate (type IV allergy) is an extremely rare condition with few reported cases. VenaSeal™, marketed as N-Butyl-2-Cyanoacrylate, is used for endovenous treatment by delivering the adhesive into the vessel. As proposed by others, a type IV allergic reaction is unlikely. Therefore, if an allergic reaction occurs after CAC treatment, the explanation could be a displacement of adhesive intracutaneous. N-Butyl-2-Cyanoacrylate is biocompatible and shows a slow, but complete hydrolytic degradation over a period of three years, accompanied by a giant cell reaction, mild chronic inflammation and cicatrices [32]. Our data indicate that the risk of general allergic reaction to CAC may be overestimated by far.

We noticed reddening of the skin, interpreted as histamine dependent hypersensitivity, typically within the first postoperative weeks, mainly after treatment of more superficially positioned veins of larger diameter. In our experience, local anti-inflammatory treatment, cooling or selective use of compression stockings was sufficient to cope with symptoms in most cases. In our experience, information of the patient and prophylactic measures contributed to a declining incidence of this complication over time. We observed systemic allergic symptoms in one patient; however, there were no septic reactions as it has been reported by Lew, when glue was used in contamination with open wounds or simultaneously with sclerosant in side branches. In selected cases, we tried to prevent subcutaneous displacement of adhesive by sheathing the white delivery catheter while it is withdrawn through the skin, as recommended [33-37].

The CAC method was in 2011 in Europe and received FDA-approval in 2015. In Germany, informed consent to a planned operation includes explicit information concerning alternative methods not associated with distinct risks, discomfort and expectations for sanitation, as long as different procedures are otherwise indicated and in common medical use. Therefore, our results may have implications for choice of methods with respect to medico legal reasons.

Obviously, our study in its retrospective approach is limited by the fact that follow-up data are incomplete. Centre-related differences in patient numbers, treatment protocols, diagnostic work-up and interpretation of clinical findings may contribute to further limitations but reflect the "real-life" conditions beyond protocols controlled prospective studies. Nevertheless, the latter are required to further evaluate pros and cons in comparison to other minimal invasive techniques currently used for GSV/SSV insufficiency.

CONCLUSION

This is the first multicenter eight-year review, demonstrating long-term effectiveness of the proprietary CAC system. The use of VenaSeal™ to treat venous reflux in truncal veins and associated varicosities results in high closure rates and 96,1% recanalization-free survival. Benefit of the treatment with cyanoacrylate closure system is less postoperative discomfort and rapid recovery even in patients who after a few days return to work or are otherwise burdened by prolonged orthostatic charge.

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